REMARKS

Claims 43-48, 50, 58-60 and 62-78 were pending in the application. Claim 58 has been canceled without prejudice and claims 43, 45-48, 67 and 78 have been amended. New claims 79-80 have been added. Accordingly, claims 43-48, 50, 59-60 and 62-80 will remain pending upon entry of the instant amendment.

Support for the claim amendments and new claims can be found in the original claims and specification as filed. No new matter has been added by way of these amendments.

The foregoing claim amendments and cancellations should in no way be construed as an acquiescence to any of the Examiner's rejections and were made solely to expedite prosecution of the present application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Restriction Requirement

Applicants gratefully acknowledge that Groups III and IV have been reformed into a single group comprising claims 43-48, 50, 58-60, and 62-78, drawn to methods of modulating growth of tumor cells *in vivo* in a subject comprising the step of administering an antibody that binds Cripto. Applicants understand that the claims are being examined to the extent that the Cripto polypeptide sequence is SEQ ID NO:1 and the tumor is breast and the hybridoma producing the antibody is B3F6.17.

Objections to the Claims

The Examiner has objected to claims 46-48, 50, 62, 70 and 73-78 as consisting of non-elected inventions. Applicants respectfully submit that, as acknowledged by the Examiner, the species of "SEQ ID NO: 1," the hybridoma "B3F6.17" and "breast tumor cells" have been elected for search purposes only. It is Applicants' understanding that the search will be extended to the remaining species upon a finding of allowability. Accordingly, the claims have not been amended so as to be directed solely to the elected species at this time.

Rejection of claims 43, 50, 58-60, and 62-78 Under 35 USC § 112, second paragraph.

Claim 43

The Examiner has rejected claim 43 as being indefinite in the recitation of "a method of modulating growth of tumor cells" and alleges that the exact meaning of the word modulate is unclear. Claim 43, as currently amended, recites "a method of inhibiting growth of tumor cells," thereby rendering the rejection moot.

Claims 46, 47, 62, 70, 74, and 78

The Examiner has rejected claims 46, 47, 62, 70, 74 and 78 as being indefinite in the recitation of "epitope of Cripto comprised in the domain spanning amino acid residues" and alleges that the exact meaning of the word spanning is unclear. Applicants respectfully traverse this rejection.

Applicants respectfully refer the Examiner to the common definition of the term "span," *e.g.*, as defined in the Hyperdictionary on the world wide web, as being "the distance or interval between two points." Applicants submit that, based on the common meaning of the term "span," it would have been clear to one of skill in the art that a "domain spanning amino acid residues from about amino acid 46 to about amino acid 62" is intended to mean a domain that begins at about amino acid 46 and ends at about amino acid 62. Thus, based on the plain meaning of the term, one of skill in the art would find the claims clear and definite.

In view of the foregoing, Applicants respectfully request that the rejection of claims 46, 47, 62, 70, 74 and 78 for indefiniteness be reconsidered and withdrawn.

Claim 67

The Examiner has rejected claim 67 as being indefinite in the recitation of "with a nonconjugated chemotherapeutic" and alleges that "it is not clear as to what a nonconjugated chemotherapeutic is." Applicants respectfully disagree. The specification defines a nonconjugated chemotherapeutic at pages 16, lines 13-23:

> ***Chemotherapeutic agents may be used in combination with the antibodies of the invention, rather than being conjugated thereto (i.e. nonconjugated chemotherapeutics)***, include, but are not limited to the following: platinums (i.e. cis platinum), anthracyclines, nucleoside analogs (purine and pyrimidine), taxanes, camptothecins,

> epipodophyllotoxins, DNA alkylating agents, folate antagonists, vinca alkaloids, ribonucleotide reductase inhibitors, estrogen inhibitors, progesterone inhibitors, androgen inhibitors, aromatase inhibitors, interferons, interleukins, monoclonal antibodies, taxol, camptosar, adriamycin (dox), 5-FU and gemcitabine. ***Such chemotherapeutics may be employed in the practice of the invention in combination with the antibodies of the invention by coadministration of the antibody and the nonconjugated chemotherapeutic.*** (page 16, lines 13-23 of the specification)

Applicants submit that based on the teachings in the specification, it would be clear to one of skill in the art that a nonconjugated chemotherapeutic is intended to mean a chemotherapeutic agent that is not conjugated to the antibodies of the invention. Notwithstanding the foregoing, in the interest of expediting prosecution and in no way acquiescing to the Examiner's rejection, claim 67 has been amended to recite "administered in combination with a chemotherapeutic agent which is not conjugated to the antibody," thereby rendering the rejection moot.

Claim 76

The Examiner has rejected claim 76 as being indefinite in the recitation of "antibody specifically binds to a Cripto amino acid which inhibits the interaction of Cripto and ALK4" and alleges that it is not clear as to how the binding of the antibody to Cripto inhibits its interaction with ALK4. Applicants respectfully disagree.

The essential inquiry pertaining to an indefiniteness rejection is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the ***content of the particular application disclosure***, (2) the teachings of the prior art, and (3) the ***claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art*** at the time the invention was made. *In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1973). MPEP 2173.02.

Applicants submit that the phrase "inhibits the interaction of Cripto and ALK4" would be clear and definite to one of skill in the art. The specification teaches at page 13, lines 11-15:

> As used herein, the term "blocking the interaction between Cripto and ALK 4" means an increase or decrease in the interaction, i.e. binding,

> between Cripto and ALK4, by about 5%, preferably 10%, more preferably 20%, more preferably 30%, more preferably 40%, more preferably 50%, more preferably 60%, more preferably 70%, more preferably 80%, more preferably 90%, and most preferably 100%,. Activity may be measured by assays known in the art, such as the binding assay shown in Example 8.

The specification teaches assays, at least in Example 8, at page 38, lines 1-22, that can be used to assess whether Cripto-specific antibodies inhibit Cripto's ability to bind to Alk4. Such binding assays were routine in the art at the time of the invention. One of skill in the art would understand that any antibody specific for Cripto and which ***prevents the interaction of Cripto with Alk4***, *e.g.*, as assessed by using any binding assays known in the art, irregardless of the precise molecular mechanism by which the interaction is inhibited, would be encompassed by the claim. Thus, one of skill in the art would find the claims clear and definite.

In view of the foregoing, Applicants respectfully request that the rejection of claim 76 for indefiniteness be reconsidered and withdrawn.

Rejection of claims 48, 71, 72, 77, and 78 Under 35 USC § 112, first paragraph.

Claims 48, 71, 72 and 78

The Examiner has rejected claims 48, 71, 72, 77 and 78 under 35 USC § 112, first paragraph for lack of enablement. The Examiner states that the "specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public: (2) reproducible from the written description" and that "a suitable deposit for patent purposes is suggested." This rejection is respectfully traversed.

In particular, the Examiner states that "[i]t is unclear if a cell line which produces an antibody having the exact chemical identity of B3F6.17 is known and publicly available, or can be reproducibly isolated without undue experimentation." In addition, the Examiner states that "[t]he specification lacks complete deposit information for the deposit of the B3F6.17 antibody."

Responsive to the rejection, the specification has been amended and copies of the deposit information for hybridomas A27F6.1, A10B2.18, A18B3.11, B6G7.10, A17G12.1, A8H3.1, A40G12.8, A8G3.5, A6F8.6 and B3F6.17 and the deposit

contract are being submitted herewith. In addition, a declaration regarding the deposits is submitted herewith. Accordingly, Applicants respectfully request that the rejection of claims 48, 71, 72, 77 and 78 under 35 USC § 112, first paragraph be reconsidered and withdrawn.

Claim 78

The Examiner has rejected claim 78 for lack of written description as containing new matter. In particular, the Examiner states that the phrase "wherein the antibody binds to an epitope comprised in the domain spanning amino acid residues 77-111 of SEQ ID NO:1" is not disclosed in the specification.

In the interest of expediting prosecution and in no way acquiescing to the Examiner's rejection, claim 78 has been amended to recite "wherein the antibody binds to an epitope comprised in the extracellular domain spanning amino acid residues 31-188 of SEQ ID NO:1." Support for this amendment can be found at least at page 9, lines 8-10 and page 17, lines 10-15. In view of the amendment to claim 78, this rejection has been rendered moot.

Rejection of Claims 43, 44-47, 50, 58-60, 62-70, 74, 76 and 78 Under 35 USC § 103(a).

Claims 43, 44-47, 50, 58-60, 62-70, 74, 76, and 78 have been rejected under 35 USC § 103(a) as being unpatentable over Qi *et al.* in view of Meissner and Coleman, in view of Williams *et al.*, in view of Dan *et al*, and further in view of Chari *et al.* This rejection is respectfully traversed.

The Examiner states that Qi *et al.* teach the expression of cripto-1 (CR-1 in human breast carcinomas." The Examiner further states that "Qi et al. also teach that the generation of an (sic) CR-1 antibody (CR-1 Ab) was generated against a 17-mer synthetic peptide that corresponds to amino acid residues 97-113 in the human CR-1 proteins that represents the carboxy terminus of the 37 amino acid EGF-like region, and that the CR-1 Ab reacts strongly with the 17-mer CR-1 peptide immunogen and the therapeutic advantages of such CR-1 antibodies (please see entire document)."

The Examiner further relies on the teachings of Meissner and Coleman as allegedly teaching "human Criptin Growth Factor polypeptide (CGF) (SEQ ID NO:7, that is 100% identical to SEQ ID NO:1 of the instant application." The Examiner

further states that Meissner and Coleman reference teaches "antagonist against such polypeptides, wherein the potential CGF antagonist compounds includes antibodies."

The Examiner further relies on Williams *et al.* for allegedly teaching that "a cripto mutant which is different from that CRIPTO polypeptide, has the ability to block or inhibit CRIPTO binding to a CRIPTO binding partner, such that the inhibition of CRIPTO binding to a CRIPTO binding partner by the cripto mutant can inhibit the growth of a tumor cell."

The Examiner further relies on Dan *et al.* as allegedly teaching "a monoclonal antibody H11 and antigen binding fragments that specifically bind to the antigen recognized by H11, the C-antigen which is found specifically on neoplastic cells and not on normal cells."

Finally, the Examiner relies on the Chari *et al.* as allegedly teaching "antibody drug-conjugates utilizing Maytansinoids as a conjugate."

The Examiner contends that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have produced a method of modulating growth of tumor cells in vivo in a subject comprising the step of administering to the subject an effective amount of an antibody that binds Cripto and a pharmaceutically acceptable carrier. The Examiner states:

> One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have used the antibodies to cripto-1 for therapeutic advantages, specifically in breast tumor, based on the teachings of Qi et al. and Meissner and Coleman because Qi et al teach the expression of cripto-1 in human breast carcinomas, in addition that the breast carcinomas express multiple EGF-related peptides and show that the differential expression of Cr-1 in malignant breast epithelial cells may serve as a potential tumor marker for breast cancer including the generation of an CR-1 antibody. . . .

The pending claims are directed to methods of inhibiting proliferation tumor cells in a subject comprising the step of administering to the subject an effective amount of a composition comprising a monoclonal antibody that binds to Cripto and a pharmaceutically acceptable carrier.

The pending claims are further directed to methods of treating a subject having a tumor that over-expresses Cripto comprising administering to the subject a

composition comprising a monoclonal antibody that binds to Cripto and a pharmaceutically acceptable carrier in an effective amount.

The pending claims are still further directed to methods of treating a subject having a tumor that over-expresses Cripto comprising administering to the subject a composition comprising a monoclonal antibody that specifically binds to an epitope of Cripto comprised in the domain spanning amino acid residues from about amino acid 46 to about amino acid 62 of SEQ ID NO:1 or SEQ ID NO:2 in an effective amount.

The pending claims are also directed to methods of treating a subject having a tumor that over-expresses Cripto comprising administering to the subject a composition comprising a monoclonal antibody that specifically binds to an epitope of Cripto comprised in the cysteine-rich domain of Cripto spanning from about amino acid residue 114 to about amino acid residue 150 of SEQ ID No:1 or SEQ ID NO:2 in an effective amount.

The pending claims are also directed to methods of treating a subject having a tumor that over-expresses Cripto comprising administering to the subject a composition comprising a monoclonal antibody which binds specifically to an epitope selected from the group of epitopes to which antibodies produced by hybridomas A6C12.11, A6F8.6, A7H1.19, A8F1.30, A8G3.5, A19A10.30, A10B2.18, A2D3.23, A7A10.29, A9G9.9, A15C12.10, A15E4.14, A17A2.16, A17C12.28, A17G12.1, A17H6.1, A18B3.11, B3F6.17, and B11H8.4 bind in an effective amount.

To establish a *prima facie* case of obviousness for the claimed invention, there must have been some ***suggestion or motivation***, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner proposed by the Examiner. Second, there must have been a ***reasonable expectation of success*** at the time the invention was made. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143.

As set forth above, the instant invention relates to methods of inhibiting proliferation of tumor cells and ***methods of treating a tumor using monoclonal antibodies*** that bind to Cripto or to specific epitopes in Cripto. In contrast, the Qi *et al.* reference discloses peptide-specific polyclonal antibodies that are capable of detecting Cripto peptides in formalin-fixed paraffin-embedded tissues and their use in ***immunocytochemistry*** to ascertain if the peptides can be localized in mammary

epithelial cells and to determine if there is any differential expression of these peptides between non-involved and malignant breast tissues. (See page 904, column 1, first full paragraph of the reference). Therefore, contrary to the Examiner's assertion that the reference teaches "the therapeutic advantage of such CR-1 antibodies (please see entire document)," Applicants submit that the reference discloses only immunocytochemistry using a polyclonal anti-Cripto antibody and is devoid of any teaching that anti-Cripto antibodies could be used therapeutically to inhibit the growth of tumor cells. Indeed, while the Qi *et al.* reference teaches that Cripto is expressed on certain cancer cells, it further discloses that the ***significance of CR-1 as a breast tumor marker "is unclear since a recombinant protein is not available to determine whether the CR-1 protein has any biological activity.***" (See page 908, column 2, first paragraph). If the Examiner insists on maintaining this rejection, the Examiner is respectfully requested to point to a specific passage of the reference where such therapeutic methods are taught or suggested.

Therefore, the primary reference cited by the Examiner fails to teach or suggest the use of monoclonal antibodies that bind to Cripto to inhibit tumor cell proliferation or to treat a subject as required by the pending claims. Moreover, the Qi *et al.* reference does not teach or suggest ***monoclonal*** antibodies that bind Cripto, as required by the pending claims. Furthermore, the ***polyclonal*** antibody disclosed in the Qi *et al.* reference was generated against a synthetic peptide corresponding to ***amino acids 97-113*** of Cripto. Therefore, the Qui *et al.* reference does not teach or suggest ***monoclonal*** antibodies that bind to a ***domain*** of CRIPTO found in ***amino acids 46-62*** or ***amino acids 114-150,*** as required by claims 46, 62, 70 and 47, 74, respectively.

The Meissner and Coleman reference fails to make up for the deficiencies in the primary reference. Meissner and Coleman disclose the use of antagonists against human ***Criptin Growth Factor polypeptide*** (***CGF***). The sequence of ***CGF*** is presented in ***SEQ ID NO:2*** of the Meissner and Coleman reference, and not in SEQ ID NO:7, as stated by the Examiner. (See column 1, lines 34-38 and column 2, lines 31-41 of Meissner and Coleman). The sequence of SEQ ID NO: 2 in the Meissner and Coleman reference encoding "Criptin Growth Factor" displays only 21.6% identity to Cripto (SEQ ID NO: 1 of the instant application and also presented in SEQ ID NO: 7 of the Meissner and Coleman reference) over its full length and is 52% identical to Cripto in a 69 amino acid overlap. An alignment of the CGF and Cripto sequences is shown in Figure 2 of the reference. (See column 2, lines 38-41).

Although Meissner and Coleman disclose making antagonists of CGF, the reference does not teach or suggest methods of inhibiting tumor cell proliferation or treating a subject using antagonists of ***Cripto***, let alone ***monoclonal antibodies to Cripto*** as required by the presently pending claims. Accordingly, the Meissner and Coleman reference fails to make up for the deficiencies of the primary reference.

The Williams *et al.* reference discloses that the growth of tumors which depend on Cripto for growth can be inhibited by ***non-fucosylated mutants*** of Cripto. The Williams reference claims priority to a provisional application filed on September 18, 2000 and the instant application claims priority to a provisional application dated April 26, 2001. Accordingly, the Examiner applies the reference as prior art under 35 U.S.C. §102(e). However, pursuant to 35 U.S.C. §103 (c) (1):

> [s]ubject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation to assignment to the same person.

As the Williams application and the instant application were, at the time the invention was made, owned by, or subject to an obligation of assignment to the same organization, the reference may not properly be applied under 35 U.S.C. §103.

The Dan *et al.* reference discloses the monoclonal antibody H11 and antigen binding fragments that specifically bind to the antigen recognized by H11, the C antigen. The reference fails to teach or suggest the use of an anti-Cripto antibody to inhibit proliferation of tumor cells or to treat tumors.

The Chari *et al.* reference discloses antibody drug-conjugates utilizing maytansinoids as a conjugate. The reference fails to teach or suggest the use of an anti-Cripto antibody to inhibit proliferation of tumor cells or to treat tumors.

Accordingly, neither the primary nor the secondary references properly applied by the Examiner (i.e., the Meissner and Coleman, the Dan, and the Chari reference) teach or suggest antiboies to Cripto, let alone using such antibodies in the presently claimed methods. It is Applicants' further position that the Examiner has failed to set forth adequate evidence of a motivating force which would have *impelled* one of ordinary skill in the art to combine the teachings of the secondary references

with Qi et al. to arrive at the claimed invention. Absent Applicants teachings, there was no motivation present in the cited art to use a monoclonal antibody that binds Cripto to inhibit tumor cell proliferation. As discussed above, the Qi *et al.* reference teaches that although Cripto is ***expressed*** on breast cancer cells, the ***significance*** of CR-1 as a ***breast tumor marker "is unclear*** since a recombinant protein is not available to determine ***whether the CR-1 protein has any biological activity***" (page 908, column 2, first paragraph). Thus, based on the disclosure of Qi *et al.* which teaches that no activity had been ascribed to Cripto, one would clearly not have been motivated to antagonize an unknown Cripto activity to inhibit proliferation of tumor cells.

With respect to the other references cited by the Examiner, each of these references fails to teach or suggest the claimed methods. In fact, none of the secondary references teaches or suggests any anti-Cripto antibody, let alone use of such an antibody in the claimed methods. The CGF target taught by Meissner and Coleman and C antigen target taught by Dan are different from Cripto and, therefore, would not have motivated one of ordinary skill in the art to arrive at the claimed invention given the disclosure of Qi et al which does not ascribe any function to Cripto and which does not teach or suggest any methods of treatment. The Cari reference discloses that Maytansinoids may be conjugated to antibodies, but also does not provide any teaching with respect to Cripto and, therefore, fails to provide the motivation to make the claimed invention.

In addition, even if one of ordinary skill in the art would have been motivated to make the invention, which Applicants deny, there was no reasonable expectation of success that anti-Cripto antibodies could be used to inhibit tumor cell proliferation. Given that the only reference properly cited by the Examiner which pertains to Cripto, the Qi reference, fails to suggest any function for Cripto, one of ordinary skill in the art would not have had a reasonable expectation of success in using an anti-Cripto antibody in the claimed methods to inhibit tumor cell proliferation or to treat a tumor.

In summary, Applicants submit that the Examiner has failed to point to any teaching in the Qi *et al.*, Meissner and Coleman, Dan *et al.* and Chari *et al.* references that would compel one of ordinary skill in the art to make the claimed invention. The prior art must suggest "to those of ordinary skill in the art that they ***should*** make the claimed composition or device, or carry out the claimed process" and "***[b]oth the***

suggestion and the ***reasonable expectation of success*** must be founded in ***the prior art, not in the applicant's disclosure.***" *In re Dow Chemical Co.* 837 F.2d 469. 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

In view of the foregoing, Applicants respectfully request that the rejection of claims 43, 44-47, 50, 58-60, 62-70, 74, 76, and 78 under 35 USC § 103(a) be reconsidered and withdrawn.

Rejection of Claims 43-48, 50, 58-60, and 62-78 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting.

Claims 43-48, 50, 58-60, and 62-78 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 88-104 of copending Application No. 10/945,853. Upon an indication of allowable subject matter in either of these applications, Applicants will consider filing a terminal disclaimer.

CONCLUSION

If a telephone conversation with the Applicant's Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at 617-227-7400.

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Respectfully submitted,

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